DETAILED ACTION

1. Applicant's arguments in the reply filed on 8/5/2011 is acknowledged and entered into the record.

2. Claims 26, 30-44, 46-53 are pending. Claims 30-44, 46-50 have been withdrawn.

3. Claims 26, 51-53 will be examined on the merits.

New Grounds of Rejection

(after further consideration)

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dorken et al. (US Patent 7112324) in view of Nissen et al. (PgPub 20020142964).

7. The claims are drawn to a composition comprising a polypeptide comprising at least two antigen binding sites wherein said at least two antigen binding sites are located on a single polypeptide chain and wherein one antigen binding site specifically binds the human CD3 antigen and the other binding site specifically binds to the human CD19, said polypeptide existing in both monomeric and multimeric form, and said polypeptide comprises any of SEQ ID NO:1-6, and said composition further comprises a citrate/lysine buffer pH 6.0-7.5.

8. Dorken et al. teach "single-chain multifunctional polypeptides comprising at least two binding sites specific for the CD19 and CD3 antigen" (see Abstract). Dorken et al. teach a polypeptide with binding sites specifically to human CD19 antigen and wherein said polypeptide has a sequence that is 100% homologous to SEQ ID NO: 1 (see attached alignment). Dorken et al. does not teach a citrate/lysine buffer. These deficiencies are made up for by Nissen et al.

9. Nissen et al. teach single-chain multimeric polypeptides and pharmaceutical compositions comprising said polypeptides. Nissen et al. disclose pharmaceutical compositions designed for administration "are prepared for storage as lyophilized formulations or aqueous solutions by mixing, as appropriate, the polypeptide having the desired degree of purity with one or more pharmaceutically acceptable carriers, excipients or stabilizers typically employed in the art (all of which are termed "excipients"), for example buffering agents, stabilizing agents, preservatives, isotonifiers, non-ionic detergents, antioxidants and/or other miscellaneous additives" (see paragraph [0269]). Nissen et al. further disclose buffering agents help to maintain

the pH in the range which approximates physiological conditions. Suitable buffering agents for use with the present invention include both organic and inorganic acids and salts thereof such as citrate buffers (see paragraph [0270]). Nissen et al. also disclose stabilizers, such as amino acids including arginine, lysine, and glycine (see paragraph [0273]).

10. It would have been *prima* facie obvious to one of ordinary skill in the art at the time the claimed invention was made to add a buffer to increase the stability of the polypeptide for pharmaceutical use. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success based on the teachings of Dorken et al. and Nissen et al, because Nissen et al teach buffering agents such as citrate buffer and stabilizing agents such as amino acids lysine and glycine are mixed with aqueous pharmaceutical compositions used for parenteral administration. Although pH values are not disclosed in Nissen et al., it is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). Therefore, one of ordinary skill in the art would be able to alter the pH using a citrate/lysine buffer to find the most optimum value for the composition. Therefore, it would be obvious to make a composition comprising the polypeptide taught by Dorken et al. by maintaining a pH in the range of 6-7.5 with increased stability by adding buffering and stabilizing agents such as citrate buffer and lysine for clinical applications.

All previous rejections are withdrawn in view of Applicants arguments in the reply filed 8/5/2011.

Conclusion

11. Claim 26 is rejected.

12. Claims 51-53 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MEERA NATARAJAN whose telephone number is (571)270-3058. The examiner can normally be reached on Monday-Friday, 9:00AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MN/

/LAURA B GODDARD/
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